REMARKS/ARGUMENTS

Applicant responds to the Examiner's comments using the paragraph numbering of the office action. Claim 11 has been amended to recite the elected species, *i.e.*, synuclein and fragments thereof (*see* paragraph bridging pp. 32-33, and p. 19, last paragraph.). Support for the recital that the immune response to an amyloid component includes antibodies in amended claim 11 is provided at *e.g.*, p. 13, lines 10-25. Support for an adjuvant that augments an immune response is provided at *e.g.*, p. 11, lines 10-15. Unless otherwise indicated amendments are for purposes of clarity. No amendment should be viewed as an acquiescence in any ground of rejection.

1. Traverse of the restriction requirement is maintained for the reasons previously indicated. However, the requirement is moot in view of the amendments to the claims.

3. Specification.

The specification was objected to as having informalities. Applicant has amended the specification to correct informalities and requests that the objection be withdrawn.

The cross reference to related application section has been replaced with a replacement section which provides domestic priority information for the instant case. A supplemental ADS providing domestic priority information is submitted herewith to satisfy the specific reference requirement of 35 U.S.C. § 119(e) and § 120.

The addition of page 96, which was inadvertently omitted from the instant application as filed, to the specification does not add new matter. The instant application incorporates U.S. Application No. 60/137,010 by reference (*see* p. 2, lines 5-6 of the instant application). Support for the addition of page 96 is provided at page 87, line 29 to page 88, line 20 of U.S. Application No. 60/137,010. For the convenience of the Examiner, applicant has attached pages 87 and 89 of U.S. Application No. 60/137,010 as Exhibit A.

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

The specification has also been amended to conform to five of the replacement drawing sheets submitted herewith, *i.e.*, Fig. 15A, Fig. 15B, Fig. 15C, Fig. 15D, and Fig. 15E, respectively. The paragraph beginning on page 10, line 26, has been replaced with six replacement paragraphs. The replacement paragraphs describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraph beginning on page 94, line 1, has also been amended to identify Figures 15A-15E.

The paragraphs beginning on page 91, line 17, and page 92, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in Application No. 09/201,430, filed November 30, 1998. The instant application claims priority to Application No. 09/201,430.

5. Sequence Listing.

The office action mailed November 15, 2002 enclosed a notice to comply with the sequence listing rules. On May 14, 2003, applicant brought the instant application into compliance with the sequence rules by submitting the following papers to the Office, via Express Mail Post Office to Addressee, in an envelope addressed to Mail Stop Sequence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450: a paper copy of the Sequence Listing, an electronic copy of the Sequence Listing, and an Amendment under 37 C.F.R. §§ 1.821-1.825.

6. Drawings.

Amendments to Figure 11

As requested by the Examiner, Figure 11 has been amended to add a legend. Support for this amendment can be found at page 77, line 17 to page 78, line 29 of the specification.

Amendments to Figures 15A-15E

As requested by the Examiner, the brief description of the drawings section of the specification has been amended to recite a brief description of Figs. 15A, 15B, 15C, 15D, and 15E.

Figures 15A-15E have been amended to correct an obvious error, *i.e.*, "p Malue" has been replaced with "p Value." Figure 15D as filed in the instant application discloses an alum concentration of 2μg/ml. Amended Figure 15D discloses an alum concentration of 2 mg/ml. Support for both of these amendments is provided by the informal Figure 15 as originally filed in the parent application. Thus, the amendments to the Figs. 15A-E contain no new matter.

Amendments to Figure 16

The descriptive term "Anti AB" has been replaced with the term "Anti-Abeta" to give greater clarity to the title. Support for this amendment can be found on page 92, lines 25-33 of the specification.

7. The claims have been amended to recite the elected material, namely synuclein or fragments thereof.

8-17. Rejections under 35 U.S.C. 112, first paragraph. Due to the length of this rejection applicant will address each paragraph in turn starting with paragraph 9.

9. The Examiner merely summarizes the claims. No response is required.

10. The Examiner alleges that the PDAPP mouse model does not exhibit Alzheimer's disease, Down's syndrome or other amyloidogenic disease as evidenced by Schenk and Games. Insofar as the Examiner is suggesting that the PDAPP mouse model is not a good model of Alzheimer's disease or Down's syndrome in humans, Applicant disagrees. The PDAPP mouse used in the present examples has been recognized in the art as being a major breakthrough in the production of an animal model for Alzheimer's disease. The importance and breakthrough

nature of the PDAPP mouse is indicated by the fact it was the cover story in that edition of Nature in which it was first described (Games et al., *Nature*, 373(6514): 523-527 (1995)). PDAPP transgenic mice described in Games exhibit age- and brain region-dependent development of typical amyloid plaques, dystrophic neurites, loss of presynaptic terminals, astrocytosis and microgliosis. These lesions in the PDAPP mouse brain tissue typify many of the neuropathological hallmarks associated with Alzheimer's disease. Games also describe neurodegeneration and inflammation characteristic of Alzheimer's disease, with associated Aβ plaque deposition and certain regions of afflicted brain parenchyma, are present in the mice genetically engineered with the construct. Deposition of brain deposits increases with age, as in the case of Alzheimer's disease. Thus, the PDAPP mouse does model much of the pathology seen in Alzheimer's disease patients.

The Schenk and Games references contradict rather than support the Examiner's allegations of inadequacy of the PDAPP mouse model. As noted above, Games appeared as the cover story of Nature and describes many characteristics of the PDAPP mouse that closely resemble the pathology in Alzheimer's disease. The reference concludes:

> A most notable feature of these transgenic mice is their Alzheimer-like neuropathology.... Our transgenic model... offers a means to test whether compounds that lower Aβ production and/or reduce its neurotoxicity in vitro can produce beneficial effects in an animal model prior to advancing such drugs into human clinical trials.
>
> p. 527, first column, second paragraph.

Similarly, Schenk, which also formed the cover story of the edition of Nature (*see* Schenk et al., *Nature*, 400:173-177 (1999)) in which it appeared, concludes

> Collectively, the results suggest that amyloid- β immunization may prove beneficial for both the treatment and prevention of Alzheimer's disease.
>
> p. 177 paragraph bridging cols. 1 and 2.

The validity of the PDAPP mouse as a model system for predicting effects of Aβ in humans is further confirmed by the performance of human clinical trials. The Investigational

New Drug Application ("INDA") supporting the clinical trials was based on essentially the same data as is contained in the present application. That the FDA allowed clinical trials to occur shows that it considered the preclinical evidence, including the results in PDAPP mouse, as being reasonably predictive of success in humans.

11. The Examiner alleges that administration of Aβ42 to Alzheimer's patients is not predictive of how synuclein affects patients with Parkinson's disease or any given amyloid dependent disorder. The Examiner alleges that there are no working examples relating to synuclein. The claims have been amended to specify that prevention or treatment of Alzheimer's disease for purposes of expediting prosecution in the present case. A fragment of synuclein (NAC) is a component (together with Aβ) of the plaques found in this disease (specification at paragraph bridging pp. 18-19). Therefore, insofar as the rejection is directed to diseases other than Alzheimer's disease, the rejection is moot. Insofar as the rejection is intended to apply to Alzheimer's disease, the specification does provide evidence that antibodies to synuclein produce similar results to antibodies to Aβ in clearing synuclein deposits. The specification describes an example in which antibodies to various epitopes of Aβ and antibodies to synuclein were tested in an *ex vivo* assay for capacity to clear amyloid deposits from brain tissue in the presence of phagocytic cells (*see* specification at pp. 113-117). The antibodies to Aβ were also tested in the PDAPP mouse model. The results from the *ex vivo* model show excellent correlation with those *in vivo*: antibody to Aβ that cleared deposits *ex vivo* also cleared deposits *in vivo* (*see* Table 16 at p. 116). Because antibodies to synuclein were found to clear amyloid deposits characteristic of Alzheimer's disease *ex vivo* and because of the excellent correlation between *ex vivo* and *in vivo* results shown for antibodies to Aβ, one would reasonable expect that antibodies to synuclein would also clear amyloid deposits *in vivo*.

12. The Examiner cites several papers (Lemere, Schenk, DeMattos and Raso) as evidence that therapy can be effective in removal of amyloid plaques. The Examiner does not indicate how any of this evidence detracts from enablement of the present claims. Accordingly, it is believed no response is needed.

13. The Examiner alleges one would doubt the claimed method would work due to lack of information as to specific biological actions/activities that synuclein and adjuvant would effect, lack of information how the immunogenic effect on amyloid deposition relates to symptoms of disease, and an alleged expectation that synuclein-NAC would be actively involved in amyloid deposition (citing Perutz, Masliah, and Conway). These points will be addressed in turn. The results described in the present specification that passive administration of antibodies to Aβ achieves essentially the same results as active administration of Aβ indicates that active administration of Aβ acts, at least in part, through formation of antibodies. By analogy, and from the additional data from the *ex vivo* assay referred to above, it is expected that administration of synuclein acts at least in part through the generation of antibodies. With respect to how the immunogenic effect of synuclein administration relates to symptoms of disease, one would expect similar symptomatic effects results from synuclein and Aβ in view of the similar results experienced in the *ex vivo* assay as described above.

Finally, the Perutz, Masliah and Conway references provide no reason to think that exogenously supplied synuclein, in combination with an adjuvant, adds to existing plaques rather than clearing plaques. Two of these references, Perutz and Conway, respectively discuss crystallographic analysis of the structure of amyloid fibers and aggregation of synuclein *in vitro*. Neither provides any reason to think exogenously supplied synuclein would aggregate into amyloid deposits *in vivo*, particularly when administered with an adjuvant as specified in the amended claims. Masliah discusses transgenic mice expressing synuclein from a platelet derived growth factor promoter. This promoter is known to express well in neural tissue. Thus, the circumstances of Masliah in which synuclein was expressed in neural tissue without an adjuvant were particularly calculated to result in synuclein deposits. This combination of conditions is excluded from the amended claims, which require an adjuvant.

14. The Examiner alleges that undue experimentation would be required to evaluate all possible aspects of both humoral and cellular aspects of the immune response. The Examiner cites Chapman, Frenkel (1999), Frenkel (1998), Frenkel (2000), and Freidland (1997)

as alleged evidence of the unpredictable effects of antigens on the immune system. In response, an understanding of mechanism is not required to practice the claim as presently formulated. The claims as presently formulated specify that one administers a dosage of synuclein or a fragment thereof effective to induce antibodies to an amyloid component derived from synuclein in combination with an adjuvant that augments the immune response. The result of treating or preventing a synuclein based disease follows from performing the claims as written without the need to understand how the induced antibodies effect this result.

It is not seen that the cited references are detrimental to enablement. Friedland discusses possible use of labeled Aβ as agent for imaging plaques in the brain. However, the Aβ is not proposed to be administered with an adjuvant or otherwise to generate an immune response comprising antibodies. Thus, there is nothing in Frenkel to suggest that the combination of Aβ and an adjuvant would not be effective in preventing or treating Alzheimer's disease. The various Frenkel references investigate the role of an N-terminal epitope of Aβ, and propose to display it from a phage for use as an immunogen to generate antibodies in a mouse model of Alzheimer's disease. This proposal appears closely related to one embodiment disclosed in the present application (which predates the Frenkel references) (*see* specification at p. 11, lines 10-14). That others have incorporated the teaching of the present application into their own work supports rather than refutes enablement of the present claims. Finally, Chapman reviews three papers that test antibodies to Aβ for effects of potential treatments of both brain damage and cognitive losses caused by Alzheimer's disease. Chapman concludes that "All in all, though, these three papers give cause for optimism" (at p. 916, first column, last paragraph). Thus, again Chapman supports rather than contradicts enablement of the present claims.

15. The Examiner alleges undue experimentation would also result from inflammatory side effects (citing to Elan press releases, Grubeck-Loebenstein, and US 5,958,883). It is respectfully submitted that requiring a patent applicant to teach means for avoiding all side effects imposes too high a standard of enablement. Here, clinical trials have indicated that inflammatory side effects may result in a small number of patients (15 out of 360), as discussed in the Elan press releases, and Munch (made of record as cite no. 359). Moreover,

in the few patients that might experience side effects, there is the possibility of mitigation by immunsuppressants (*see* Munch at p. 1085). Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Moreover, the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Ibid.*

16. The Examiner alleges additional unpredictability due to the recitation of mutant proteins, peptides. The language quoted by the Examiner appears in claim 13 in reference to precursor proteins. Because claim 13 has been cancelled, the rejection is moot. This amendment is made only to expedite prosecution and does not represent acquiescence in the Examiner's position in this or related cases. Insofar as the rejection is directed to fragments, the *ex vivo* assay provides evidence that the NAC fragment is likely to effective for treatment of Alzheimer's disease in that an antibody to NAC cleared amyloid deposits. The effectiveness of NAC fragment can also be inferred because it is the form of synuclein present in natural plaques. Other fragments of synuclein could be screened using antibodies to different epitopes of synuclein using the same *ex vivo* assay. Alternatively, fragments could be screened directly for activity in clearing plaques using the PDAPP mouse model described in the Examples. The number of fragments of synuclein is not infinite and because many of the various possible fragment of synuclein have overlapping sequences, the key regions of peptide needed for pharmacological activity can be determined by screening only a relatively small proportion of the total number of peptides. For example, if it found that deletion of 20 amino acids from the N-terminus of synuclein has no lowering of activity, then one can infer that deletions of fewer amino acids from the N-terminus will also not lower activity. Thus, by testing only a few of the possible fragments of synuclein, one can predict whether any other fragment will have pharmacological activity. Thus, it is submitted that undue experimentation would not be required to identify suitable fragments to use in the methods.

17. The Examiner alleges that the application must establish a nexus between the specific immune response recited in the claims for each amyloid disorder and the alleviation of the disease state. The Examiner alleges that the skilled artisan is not guided as to how an immune response must effectuate one or more actuates of each targeted protein such that the immune response would alleviate the disorder. The Examiner also refers to variation between different amyloid disorders (citing Small, Chapman , Esiri, St. George-Hyslop, Younkin, Tennent, and Stein). As previously discussed, the application does provide evidence that an antibody component of an immune response to peptide administration is, at least in part, responsible for alleviation of the disease state. This is shown by the result that passive immunization with antibodies achieves essentially the same results as active immunization with peptides. Further understanding of the mechanisms by which antibodies lead to clearing of amyloid deposits is not required for practice of the invention. Nevertheless, the application does provide data showing that induction of a phagocytic clearing response is involved, at least in part, in the clearing response due to antibodies to Aβ (*see, e.g.*, specification at p. 116, last paragraph). The Examiner's additional comments regarding possible variation between different types of amyloid disease are moot in view of the amendment of the claims to Alzheimer's disease.

18-19. The claims are provisionally rejected for same invention double patenting over claims of several copending cases. Applicant requests this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely in view of the restriction and election of species requirements that the claims in the cited cases will differ from those pending in the current case at the time of allowance of the present case. However, if claims from different cases are in conflict at that time, applicant will amend the claims in the cited cases to avoid the conflict.

20-27. The claims stand provisionally rejected for obviousness type double patenting over several copending cases. Applicant proposes the issues be held in abeyance until

indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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